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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/528,463	GUILLEMETTE, CHANTAL	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *25-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/10/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-15 and 17-29 are currently pending. Applicant's election without traverse of Group I in the reply filed on November 3, 2006 is acknowledged. Applicants further have elected the UGT1A9 gene without traverse and the SNP at position 275 of the UGT1A9 gene with traverse. The Applicants timely traversed the restriction (election) requirement by stating that unity of invention is fulfilled when there is technical relationship among the inventions. This argument has been fully considered but not found persuasive because the special technical feature of the present invention is SNPs in the UGT1A1, UGTA1A7, and UGTA19 genes. This special technical feature does not constitute a contribution over the prior art because the prior art teaches SNPS in UGT1A1. For example the prior art of Guillemette et al (Cancer Epidemiology, Biomarkers, and Prevention 2001 Vol 10 pages 711-714) teach the association of genetic polymorphisms in UGTIA1 gene with breast cancer and plasma hormone levels. Thus there is no special technical feature. The applicants further submit that all of the SNPs of UGTA19 should be examined together because they all have a common activity: they modify the predisposition of an individual. However each SNP causes a unique nucleic acid change which may or may not result in change in the amino acid sequence at the corresponding codon which further may or may not change the functional properties of the protein. Thus each SNP is not regarded as being of similar nature because each SNP has a different effect. Additionally searching for all of the polymorphic variations of the UGT1A9 would be an undue burden for the examiner for

the reasons stated in the Restriction Requirement issued September 5, 2006. Thus this restriction requirement is deemed proper and is now made FINAL.

Claims 18-29 been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim.

Accordingly, Claims 1-15 and 17 have been examined herein.

Claim Objections

2. Claim 17 is objected to because the claim still recites mutations which have not been elected. Appropriate changes are required.

Drawings

3. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Fig 6 is illegible. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8, and 20-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims are drawn broadly to encompass a method for determining the predisposition of an individual to a physiological reaction to a biologically active compound comprising determining the presence of a polymorphic or haplotypic variation in the nucleotide sequence of UGT1A9. The claims do not define the nucleotide variation in terms of particular structure or function

The specification at page 20 teaches 2 missense mutations in the UGT1A9 gene that result in amino acid substitutions in the UGT1A9 protein, namely the C3Y and the M33T amino acid substitutions. The mutations that result in the C3Y and the M33T substitutions occur in exon 1. The specification further teaches on page 24 ten polymorphic mutations within the UGT1A9 promoter region. The specification also teaches several haplotypes of the UGT1A9 which are presented in Table 11. It is noted that the specification teaches mutations present only in exon 1 and the promoter of the UGT1A9 gene. However, the specification does not teach any mutations in any of

the remaining exons, or in any introns or 5' or 3' non-coding sequences and does not teach any gross chromosomal rearrangements in the UGT1A9 gene. While methods which detect the nucleotide variation of the 2 missense mutation in exon 1 and the 10 mutations in the promoter region of UGT1A9 meet the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the genus required by the claims of any variation in the UGT1A9 gene.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that 'applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that 'An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, 12 members of the genus of UGT1A9 nucleotide variations have been identified. No additional nucleotide variations have been disclosed in the specification or prior art. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.). In the instant case, no such identifying characteristics have been provided for any of allelic variants or mutant UGT1A9 nucleic acids. Yet, the claims as written are inclusive of a potentially large genus of mutations in the UGT1A9 gene. While one could contemplate a nucleotide substitution, deletion or addition at each and every position in the UGT1A9 gene, such nucleotide variations are not considered to be equivalent to specific nucleotide variations associated with causing a physiological reaction to a biologically active compound. Rather, mutations in the UGT1A9 gene that do cause physiological reactions to biologically active compounds represent a distinct group of nucleotide variations which are expected to occur at only specific locations within the gene and consist of specific nucleotide alterations. Accordingly, knowledge of the sequence of the wild-type gene does not allow the skilled artisan to envision all of the contemplated polymorphisms encompassed by the claimed genus. Conception of the claimed invention cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of potential methods for isolating additional nucleotide variations. As stated in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993)

and *Amgen Inc. V. Chugai Pharmaceutical Co. LTD*, 25 USPQ2d 1016, one cannot describe what one has not conceived.

For these reasons, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 'Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

5. Claims 1-15 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claim 1 is drawn broadly to a method for determining the predisposition of an individual to a physiological reaction to a biologically active compound by determining the presence of a polymorphic or haplotypic variation in the UGT1A9 gene or part thereof. This claim reads on any individual (i.e. human, cat, mouse etc...), any type of sample, any type of physiological reaction, any biologically active compound, and any polymorphic or haplotypic variation in the UGT1A9 gene or part thereof. Claims 2-3 further define the predisposition. Claims 4-5 further define the physiological reaction. Claims 6-11 further define the biologically active compound. Claims 11-14 further define the individuals. Claim 17 defines the location of the SNP.

Nature of the Invention

The claims are drawn to a method for determining the predisposition of an individual to a physiological reaction to a biologically active compound. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches on page 1 that the UDP-glucuronosyltransferase enzymes are a set of enzymes that increase the polarity of xenobiotics, drugs, and endogenous compounds to facilitate their excretion from the body. Any perturbation in the glucuronidation pathway has the potential to modify the elimination, the detoxification or the pharmacokinetic parameters of a given drug, and consequently drug clearance. Thus human genetic variation leading to differences in the

glucuronidation rates could influence the activity of drugs and other chemicals. The specification on page 16 further teaches that DNA samples from 201 Caucasian subjects were used to genotype the UGT1A9 gene. The specification does not teach any other type of samples being used or that any non-human organisms were genotyped. The specification teaches on page 20, two missense mutations in the UGT1A9 gene that result in amino acid substitutions in the UGT1A9 protein, namely the C3Y and the M33T amino acid substitutions. The mutations that result in the C3Y and the M33T substitutions occur in exon 1. The specification further teaches on page 24 ten polymorphic mutations within the UGT1A9 promoter region. The specification also teaches UGT1A9 promoter haplotypes (See Table 11). It is noted that Table 11 teaches the frequencies of these haplotypes in the populations, however the specification does not provide any information on the percentage of linkage disequilibrium between these SNPs. Further the specification does not teach any additional mutations in any of the remaining exons, or in any introns or 5' or 3' non-coding sequences and does not teach any gross chromosomal rearrangements in the UGT1A9 gene. In addition to genotyping, the effect of UGT1A9 polymorphic variations on live microsomes glucuronidation was determined. The specification states on page 25 that there was a positive correlation between the presence of the –275 mutated alleles and higher glucuronidation rate with SN-38 (See Fig 12). It is noted that Fig 12 shows that carriers of the –275 allele have a higher glucuronidation rate than non-carriers however there is sufficient overlap on the graph and it cannot be determined if these results are significant. Additionally the specification teaches that SN-38 is the

pharmacologically active metabolite of the anticancer drug irinotecan which undergoes extensive glucuronidation in humans to form SN-38-G. The specification does not teach an association between the –275 mutated alleles and any other biologically active compound. Further the specification does not teach an association between the –275 mutated alleles and any other physiological reaction besides a higher glucuronidation rate.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying novel variants in UGT1A9 gene which are associated with higher glucuronidation rates with SN-38 is highly unpredictable. Knowledge of the sequence of the wild type UGT1A9 gene does not allow one to immediately envision additional mutations in the UGT1A9 gene that are associated with higher glucuronidation rates with SN-38. The UGT1A9 gene is expected to contain numerous polymorphisms. This finding is supported by the teachings in the post filing date art of Carlini et al (Clinical Cancer Research 2005) teaches several additional polymorphisms identified in the coding region, the promoter region, and non-coding regions of UGT1A9 (see page 1228). However, the specification does not teach a predictable means for identifying additional variations associated with a higher glucuronidation rate with SN-38. Without extensive information regarding the structure-function relationship between the UGT1A9 gene and glucuronidation, it is highly unpredictable as to what would be the identity of additional mutant, allelic, or splice variants which would be associated with a higher glucuronidation rate with SN-38.

Further, it is unpredictable as to whether the results obtained in human subjects could be extrapolated to other organisms. Knowledge that the –275 mutation in the UGT1A9 gene occur in humans does not allow one to conclude that this gene, and this mutation in this gene will also occur in other organisms and will be associated with a higher glucuronidation rate with SN-38. The specification does not teach homologues of the UGT1A9 gene in a representative number of different organisms. In the absence of information regarding the functional properties of the UGT1A9 gene and the disclosed mutations in this gene, it is unpredictable as to whether the UGT1A9 gene, and particularly the T275A mutation, will also be present in other organisms and will be associated with a higher glucuronidation rate with SN-38.

It is also unpredictable as to whether the results obtained with SN-38 can be extrapolated to other biologically active compounds. SN-38 is the pharmacologically active metabolite of the anticancer drug irinotecan. The teachings in the specification are limited to an association between the –275 mutation and a higher glucuronidation rate with SN-38. There are no teachings in the specification regarding the –275 mutation and the glucuronidation rate of other drugs, particularly anticancer drugs. Accordingly, it is unpredictable as to whether the presently claimed method can be used to determine the predisposition of any individual to any biologically active compound.

Amount of Direction or Guidance Provided by the Specification:

The specification teaches that the –275 mutation of the UGT1A9 gene is associated with higher glucuronidation rates with SN-38. To identify additional variants of the UGT1A9 gene which are associated with higher glucuronidation rates with SN-38

and other biologically active compounds would require extensive experimentation. For example, such experimentation may involve sequencing the UGT1A9 gene of individuals and then exposing them to SN-38 or other biologically active compounds and then determining the glucuronidation rates. The results of performing such methodology is highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional variants of the UGT1A9 gene which are associated with higher glucuronidation rates.

Working Examples:

Again the specification teaches the –275 mutation of the UGT1A9 gene is associated with higher glucuronidation rates with SN-38. There are no specific examples provided in the specification in which the –275 mutated alleles were associated with a higher glucuronidation rates with any other biologically active compound. Further there are no specific examples provided in the specification in which the –275 mutated alleles were associated with any other type of physiological reaction with SN-38. Additionally there are no specific examples in which non-human organisms were used.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he

scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims are not enabled because the specification does not teach a representative number of variants of the UGT1A9 gene which are associated with a higher glucuronidation rate with SN-38. The specification does not teach any additional physiological reactions associated with this mutation or that this mutation is associated with a higher glucuronidation rate with any other biologically active compounds. Additionally, the disclosure of a single organism (i.e. humans) is not representative of the broadly claimed genus of any individual. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Conclusion

6. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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SUPERVISORY PATENT EXAMINER

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